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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,861	COLOMBO ET AL.	
	Examiner	Art Unit	
	SATYANARAYANA R. GUDIBANDE	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 17-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 17-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1/3/07, 1/19/07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

No election restriction has been made in the instant application.

Claims 17-22 are pending.

Claims 17-22 are examined on the merit.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 20, 21 and 22 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Stahl, et al., 2002, International Journal of Pharmaceutics, 233, 227-237.

In the application, applicants claim a stable microparticle of insulin optionally in association with excipients obtained by spray drying an aqueous solution of insulin having an acidic pH under the isoelectric point (5.4) of insulin, concentration of insulin being 5-100 mg/ml and particles having a d90 volume lower than 9 μm.

The instant claims are interpreted as product by process claims and according to MPEP, section, 2113 [R-1], "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

The reference of Stahl, et al., discloses process of preparing microparticles of inhalable insulin via spray drying. The reference has studied various process variables on the degradation and physical properties of spray dried insulin intended for inhalation and hence the reference teaches the process variables for making stable microparticles that indicated that outlet air temperature be kept below 120 0C to avoid degradation during the spray drying process (Abstract, page 236, column 2, under the section "Conclusion"). The reference also teaches that the insulin was dissolved in distilled water to obtain a solution with pH below the isoelectric point (pH 5.4) and the concentration of the

solution held at 5 mg/ml (page 228, column 2, paragraph 2) that reads on the concentration limitations 5-100 mg/ml of instant claim 1. The cited reference also teaches that the mass median diameter of the particles were within the range 1.6-4.4 μm (page 232, bridging paragraph between columns 1 and 2), that is within the recited value of 9 μm and according to the figure 1 on page 232, almost all of the particles has a diameter between 1.6-4.4 μm reading on the instant limitation that 80% of them has an aerodynamic diameter lower than 5 μm. Also, the figure 1 illustrates that 90% of the particles exhibits dimensions of 1.6-4.4 μm in diameter and hence reads on the instant claim 1 limitation of d90 volume. Since the insulin is dissolved in distilled water, the contents of the salt in the solution for spray drying will noticeably be less than 10% by weight. Since the reference teaches the process for preparing microparticles of insulin for inhalation, it is suitable as pharmaceutical composition and hence reads on instant claims 21 and 22. The scanning electron microscopic pictures on page 233 of the particles clearly illustrates that the particles are amorphous in nature (not crystalline) and hence reads on the limitation of instant claim 20.

The reference does not explicitly teaches that the aqueous solution of insulin be prepared in aqueous solution of acetic acid. Since the cited reference of Stahl., teaches the effect of process variables on the degradation and physical properties of spray drying of insulin, one of ordinary skill in the art would look at the effect of varying the pH of the spray drying solution on the stability of the microparticles of insulin. Hence where applicants claim a process of preparation of insulin by spray drying not explicitly taught by the cited reference of Stahl, a rejection under 35 USC 102(b)/103 is proper (MPEP 2113 [R-1]).

Claims 17 and 20-22 are rejected under 35 U.S.C. 103(a) as obvious over Stahl, et al., 2002, International Journal of Pharmaceutics, 233, 227-237 further in view of US 2002/0052310 A1 of Edwards.

Stahl does not explicitly disclose that the insulin was in an aqueous solution of acetic acid for spray drying in the process of preparing the microparticles.

The reference of Edwards, discloses that particles of insulin can be prepared by spray drying wherein the insulin may be dissolved in aqueous buffer system such as acetate [0126]. The reference also discloses that the pH of the insulin solution may be adjusted to about 4.0 wherein the insulin molecules will have a net negative charge.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Stahl and Edwards to arrive at the instant invention wherein each the references teaches microparticle formation using spray drying of insulin. One would have been motivated to do so given the fact that Stahl studied factors that influence the stable particle formation during spray drying and Edwards taught that the spray drying of insulin can be performed by dissolving insulin in acetate buffer.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary

skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stahl, et al., 2002, International Journal of Pharmaceutics, 233, 227-237 in view of US 2002/0052310 A1 of Edwards as applied to claims 17 and 20-22 above, and further in view of US 2003/0165436 A1 of Stainforth.

The cited reference of Stahl and Edwards does not teach mannitol as an excipient in the spray drying of insulin.

The reference of Stainforth, discloses that mannitol can be used as a carrier particle in the preparation of inhalable formulations [0017] wherein the active ingredient is insulin [0037]. The cited reference of Stainforth also discloses that the tapped density of the carrier particles not more than 0.7 g/cc [0024]. Although, the reference teaches the tapped density of the carrier particles, the term 'tapped density' refers to the inherent physical property of a particulate matter that has a certain mass and volume [0025] and could be altered by manipulating the size and weight of the particle. Since the particle size of the microparticle of Stahl reads on the particle size limitation of the instant application and hence reads on instant claim 18.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the spray drying method of Stahl and Edwards to incorporate the excipient mannitol as a carrier of Stainforth to achieve a tapped density lower than 0.2 g/cc. One would have been motivated to do so to improve the stability of the particles because the incorporation of carrier particles imparts excellent flow

properties to formulations [0021]. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654